A Simple, Unambiguous Synthesis of 2-Amino-4-oxo- and -4-thioxo-3,4-dihydropyrimidine-5-carbonitriles

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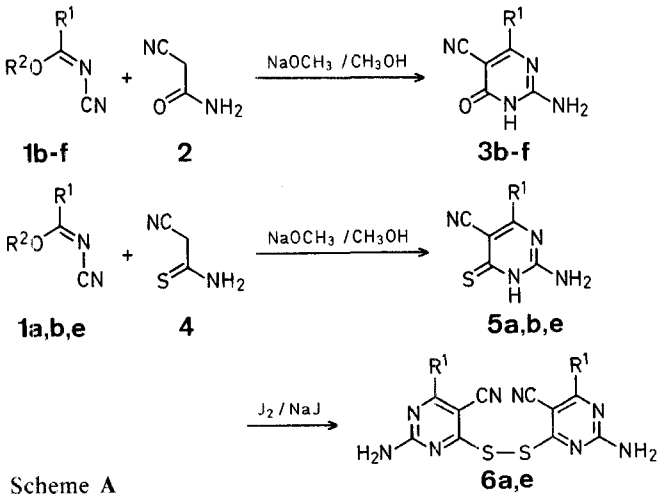
The few reported syntheses of 2-amino-4-oxopyrimidine-5-carbonitriles use the reaction of guanidine with polyfunctional compounds carrying a carbonitrile and an ester group. Either group can participate in the cyclization and the outcome of the reaction depends on the substitution of the educt[1,2,3]. On the other hand, no route to 2-amino-4-thioxopyrimidine-5-carbonitriles has been reported to date. Now we communicate a simple and unambiguous synthesis of 2-amino-4-oxo- (3) or -4-thioxo-3,4-dihydropyrimidine-5-carbonitriles (5) from the versatile[4] alkyl *N*-cyanoimidates 1 and 2-cyanoacetamide or 2-cyanoethanethioamide 2 or 4.



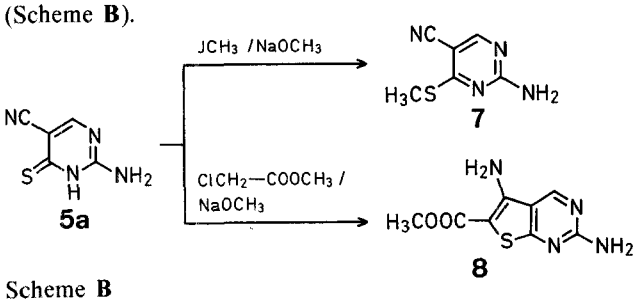
Scheme A

Alkyl *N*-cyanoimidates 1 can be prepared from cyanamide and ortho esters[5] or imidate hydrochlorides in methanolic (restricted to *N*-cyanoalkanimidates)[5] or aqueous medium[6]. The use of the latter procedure[6] for preparation of other representatives gave in our hands not reproducible, often negligible yields. This was probably due to the lack of an accurate control of the acidity of the reaction mixture and the occurrence of several pH-dependent competitive processes.

A detailed study of the reaction of cyanamide with imidate hydrochlorides or free imidates in different buffers at narrow pH-intervals was undertaken. Under acidic conditions the hydrolysis of the imidate to ester prevailed, while at basic conditions *N*-cyanoamidine[7] formation took place. Conditions which allow reasonable yields and minimum excess of buffer were reached using an interval of 0.6 units around the pH of a mixture of equimolar amounts of NaH_2PO_4 and Na_2HPO_4 in water.

By refluxing equimolar amounts of the *N*-cyanoimidates **1b-f** and 2-cyanoacetamide **(2)** with 1.1 molar equivalents of sodium methoxide in dry methanol the 4-oxo-3,4-dihydropyrimidine-5-carbonitriles **3b-f** were isolated pure after a simple work up (Table 2). An analogous reaction of equimolar amounts of the *N*-cyanoimidates **1a, b, e** and 2-cyanoethanethioamide **(4)** with an excess of sodium methoxide in refluxing methanol afforded the 4-thioxo-3,4-dihydropyrimidine-5-carbonitriles **5a, b, e.** Two of them were oxidized with iodine and sodium iodide to the disulfides **6a, e.** The disulfide **6e** was also obtained from a reaction mixture of **5e** left exposed to the air for several days (Scheme **A**). The oxidation of the 4-thioxo-3,4-dihydropyrimidines **5** could be prevented by isolating them after formation or by adding 2-mercaptoethanol to their solutions[8].

On treating a solution of the sodium salt of the 2-amino-4-thioxo-3,4-dihydropyrimidine-5-carbonitrile **(5a)** with an excess of iodomethane at room temperature 2-amino-4-(methylthio)-pyrimidine-5-carbonitrile **(7)** precipitated and was collected by filtration. The reaction of equimolar amounts of the pyrimidine **5a** and methyl chloroacetate with an excess of sodium methoxide in refluxing methanol led to methyl 2,5-diaminothieno[2,3-*d*]pyrimidine-6-carboxylate **(8)** through a nucleophilic substitution and an intramolecular cyclization (Scheme **B**).



Scheme **B**

Methyl *N*-Cyanoimidates 1c-f; General Procedure:
The methyl imidate hydrochloride (0.2 mol) is added in portions over 5 min to a mixture of Na_2HPO_4 (56.8 g, 0.4 mol), $NaH_2PO_4 \cdot H_2O$ (27.6 g, 0.2 mol), and cyanamide (9.3 g, 0.22 mol) in water (150 ml) and stirring is continued for 16 h at room temperature. The reaction mixture is diluted with water (250 ml) and extracted with dichloromethane (2 × 100 ml). The combined organic layer is washed with water (100 ml), dried with magnesium sulfate, and evaporated. The residue is distilled at reduced pressure to yield the methyl *N*-cyanoimidates **1c-f** (Table 1).

6-Alkyl(or aryl)-2-amino-4-oxo-1,4-dihydropyrimidine-5-carbonitriles 3b-f; General Procedure:
A solution of methyl *N*-cyanoimidate **1** (10 mmol), 2-cyanoacetamide

Table 1. *N*-Cyanoimidates **1a-f**

Product	R^1	R^2	Yield [%]	b.p. [°C]/torr	Molecular Formula[a] or Lit. b.p. [°C]/torr	I.R. (Film) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4) δ [ppm]
1a	H	C_2H_5	74	80–81°/0.5	58–63°/0.1[5]	2200, 1620	8.30 (s, 1H, HC=N); 4.30 (q, J=7 Hz, 2H, CH_2O); 1.37 (t, J=7 Hz, 3H, CH_3)
1b	CH_3	CH_3	54	56–58°/2	98–99°/25[5]	2200, 1610	3.77 (s, 3H, CH_3O); 2.33 (s, 3H, CH_3)
1c	C_2H_5	CH_3	32	53–54°/0.8	$C_5H_8N_2O$ (112.1)	2220, 1610	3.83 (s, 3H, CH_3O); 2.70 (q, J=7 Hz, 2H, CH_2); 1.28 (t, J=7 Hz, 3H, CH_3)
1d	$C_6H_5CH_2$	CH_3	58	105–108°/0.1	$C_{10}H_{10}N_2O$ (174.2)	2220, 1610	7.03 (s, 5H, H_{arom}); 3.80 (s, 2H, CH_2); 3.60 (s, 3H, CH_3O)
1e	C_6H_5	CH_3	59	103–104°/0.1	115–125°/0.3[5]	2200, 1610	7.9–7.7 (m, 2H, *o*-H_{arom}); 7.4–7.1 (m, 3H, *m,p*-H_{arom}); 3.83 (s, 3H, CH_3O)[b]
1f	4-H_3C—C_6H_4	CH_3	34	112–114°/0.1 (m.p. 57 °C)[c]	$C_{10}H_{10}N_2O$ (174.2)	2220, 1610[d]	7.8–6.9 (m, 4H, H_{arom}); 3.87 (s, 3H, CH_3O); 2.33 (s, 3H, CH_3)[b]

[a] Satisfactory microanalyses obtained: C ±0.15, H ±0.19, N ±0.21.
[b] Recorded in $CDCl_3$ solution.
[c] Recrystallized from toluene/hexane.
[d] KBr disc.

Table 2. 6-Alkyl(or aryl)-2-amino-4-oxo-3,4-dihydropyrimidine-5-carbonitriles **3b-f**

Product	R^1	Yield [%]	m.p.[a] [°C]	Molecular formula[b] or Lit. m.p. [°C]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6)[c] δ [ppm]
3b	CH_3	66	—[d]	>300°[3]	3550, 3470, 2230, 1700, 1645	11.3 (br. s, 1H, NH+OH); 7.2 (br. s, 2H, NH_2); 2.23 (s, 3H, CH_3)
3c	C_2H_5	66	316–317°	$C_7H_8N_4O$ (167.2)	3560, 3495, 2220, 1700, 1605	11.2 (br. s, 1H, NH+OH); 7.1 (br. s, 2H, NH_2); 2.47 (q, 2H, CH_2); 1.15 (t, 3H, CH_3)
3d	$C_6H_5CH_2$	71	315–316°	$C_{12}H_{10}N_4O$ (226.2)	3380, 3160, 2210, 1690, 1650	11.1 (br. s, 1H, NH+OH); 7.07 (s+br. s, 7H, $H_{arom}+NH_2$)
3e	C_6H_5	77	342–343°	340–342° (dec.)[2]	3400, 3140, 2220, 1680, 1625	11.8 (br. s, 1H, NH+OH); 8.0–7.5 (m, 7H, $5H_{arom}+NH_2$)
3f	4-H_3C—C_6H_4	60	332–333°	$C_{12}H_{10}N_4O$ (226.2)	3400, 3140, 2220, 1680, 1650	11.4 (br. s, 1H, NH); 7.7–7.1 (m, 6H, $H_{arom}+NH_2$); 2.33 (s, 3H, CH_3)

[a] All compounds decomposed on melting.
[b] Satisfactory microanalyses obtained: C ±0.21, H ±0.09, N ±0.29.
[c] All NH_2 and NH signals were exchanged with D_2O.
[d] Progressive decomposition over 300 °C; a sample introduced at 350 °C decomposed without melting.

(**2**; 0.85 g, 10 mmol), and sodium methoxide (11 mmol) in dry methanol (30 ml) is heated under reflux for 2 h. To the reaction mixture at room temperature concentrated (~18 molar) sulfuric acid (0.5 ml, ~9 mmol) is added and the solvent is evaporated. The residue is washed with water (~100 ml), collected by filtration, and recrystallized to yield the pyrimidines **3b-f** (Table 2).

6-Alkyl(or aryl)-2-amino-4-thioxo-1,4-dihydropyrimidine-5-carbonitriles 5a, b, e; General Procedure:

A solution of alkyl *N*-cyanoimidate **1** (10 mmol), 2-cyanoethanethioamide (**4**; 1.0 g, 10 mmol), and sodium methoxide (20 mmol) in dry methanol (30 ml) is refluxed for 3 h. To the reaction mixture at room temperature concentrated (~18 molar) sulfuric acid (1.5 ml, ~27 mmol) and silica gel (5 g) are added. The solvent is evaporated, the residue is eluted with ethyl acetate (500 ml) through a silica gel (40 g) column, and the first fraction (~50 ml) containing some unreacted 2-cyanoethanethioamide is discarded. Evaporation of the solvent and recrystallization of the residue from methanol or ethanol (**5b**) yields the pyrimidines **5a, b, e** (Table 3).

Bis[2-amino-(and 6-phenyl-)5-cyanopyrimidin-4-yl] Disulfides 6a, e:

A mixture of 4-thioxo-3,4-dihydropyrimidine-5-carbonitrile **5** (2 mmol), iodine (0.53 g, 2.1 mmol), sodium iodide (0.03 g, 0.2 mmol), and dry methanol (15 ml) is stirred for 3 h at room temperature. The solvent is evaporated and the residue is washed several times with water and recrystallized from ethanol (**6a**) or methanol to afford the disulfides **6a, e** (Table 3).

2-Amino-4-methylthiopyrimidine-5-carbonitrile (7):

To a solution of 2-amino-4-thioxo-3,4-dihydro-pyrimidine-5-carbonitrile (**5a**; 0.25 g, 1.64 mmol) and sodium methoxide (1.6 mmol) in dry methanol (15 ml), iodomethane (0.45 g, 3.2 mmol) is added. The mixture is stirred for 2 h at room temperature. The precipitate thus formed is collected by filtration and recrystallized from methanol; yield: 0.20 g (73%); m.p. 263–264 °C.

$C_6H_6N_4S$	calc.	C 43.36	H 3.64	N 33.71
(166.2)	found	43.13	3.53	33.92

I.R. (KBr): ν=3415, 3320, 3160, 2220, 1655 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ=8.08 (s, 1H, H_{arom}); 7.45 (br s, 2H, NH_2, exchangeable with D_2O); 2.48 ppm (s, 3H, CH_3S).

Methyl 2,5-Diaminothieno[2,3-*d*]pyrimidine-6-carboxylate (8):

A mixture of 4-thioxo-3,4-dihydropyrimidine-5-carbonitrile **5a** (0.61 g, 4 mmol), methyl chloroacetate (0.44 g, 4 mmol), and sodium methoxide (4.8 mmol) in dry methanol (30 ml) is refluxed for 3 h. The precipitate thus formed is filtered, washed with water (50 ml), and recrystallized from acetic acid/water (1:3); yield: 0.57 g (64%); m.p. 296–298 °C (dec.).

$C_8H_8N_4O_2S$	calc.	C 42.85	H 3.60	N 24.99
(224.2)	found	42.72	3.68	24.81

I.R. (KBr): ν=3470, 3360, 3300, 3150, 1655 cm^{-1} (—$COOCH_3$ hydrogen-bonded with *o*-NH_2).

^{1}H-N.M.R. (DMSO-d_6): δ=8.93 (s, 1H, H_{arom}), 7.21 (s, 2H, NH_2, exchangeable with D_2O), 7.07 (s, 2H, NH_2, exchangeable), 3.70 ppm (s, 3H, CH_3O).

Table 3. 6-Alkyl(or aryl)-2-amino-4-thioxo-3,4-dihydropyrimidine-5-carbonitriles **5a, b, e** and Disulfides **6a, e**

Product	R^1	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6)[b] δ [ppm]
5a	H	74	—[c]	$C_5H_4N_4S$ (152.2)	3420, 3060, 2240, 1670	12.1 (br. s, 1H, NH); 8.00 (s, 1H, H_{arom}); 7.4 (br. s, 2H, NH_2)
5b	CH_3	44	—[c]	$C_6H_6N_4S$ (166.2)	3340, 3060, 2220, 1670	12.2 (br. s, 1H, NH); 7.3 (br. s, 2H, NH_2); 2.27 (s, 3H, CH_3)
5e	C_6H_5	41	286–287° (dec.)	$C_{11}H_8N_4S$[d] (228.3)	3430, 3300, 2220, 1660	12.6 (br. s, 1H, NH); 7.9–7.4 (m, 7H, $H_{arom} + NH_2$)
6a	H	94	—[c]	$C_{10}H_6N_8S_2$ (302.3)	3400, 3310, 2220, 1635	8.25 (s, 2H, H_{arom}); 7.6 (br. s, 4H, NH_2)
6e	C_6H_5	87	219–220°	$C_{22}H_{14}N_8S_2$ (454.5)	3440, 3310, 2220, 1645	8.0–7.3 (m, $H_{arom} + NH_2$)

[a] Satisfactory microanalyses obtained: C ±0.19, H ±0.27, N ±0.31, S +0.25 (**5e** only).
[b] All NH_2 and NH signals were exchanged with D_2O.
[c] Progressive decomposition over 260 °C; a sample introduced at 350 °C decomposed without melting.
[d] M.S.: *m/e* (rel. intens. %) = 228 (M^+, 100), 227 (17), 201 (17), 196 (24), 187 (19), 170 (12).

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1 S. Nishigaki et al., *Chem. Pharm. Bull.* **18,** 1003 (1970).
2 M. A. Pérez, J. L. Soto, *Synthesis* **1981,** 955.
3 I. Ito, N. Ota, T. Kato, K. Ota, *Chem. Pharm. Bull.* **23,** 2104 (1975).
4 M. A. Pérez, J. L. Soto, *Heterocycles* **20,** 463 (1983).
5 K. R. Huffman, F. C. Schaefer, *J. Org. Chem.* **28,** 1816 (1963).
6 W. Lwowski, *Synthesis* **1971,** 263.
7 K. R. Huffman, F. C. Schaefer, *J. Org. Chem.* **28,** 1812 (1963).
8 A. Fava, A. Iliceto, E. Camera, *J. Am. Chem. Soc.* **79,** 833 (1957).